REMARKS/ARGUMENTS

Claims 1 to 8, 14 to 17, and 24 are pending in the application.

The Specification has been amended on page 8 to correct spelling errors and to remove an extraneous question mark. No new matter is added.

Applicant respectfully requests reconsideration of the rejections of record in view of the following remarks.

I. Maintained Rejections under 35 USC § 103(a) for Alleged Obviousness

A. The Office Action maintains the rejection of Claims 1 to 7, 14 to 17, and 24 under 35 U.S.C. § 103(a) as allegedly obvious over Tsutsumi, Y., *et al., Jpn J. Cancer Res.* 85:9-12 (1994)("Tsutsumi I") in view of Satake-Ishikawa, R., *et al., Cell Structure and Function* 17:157-160 (1992)("Satake-Ishikawa") and EP 0 401 384 ("Ishikawa").

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). The Office Action alleges that one of skill in the art would be motivated to combine the cited references as Tsutsumi I teaches TNF-modified with PEG having an average molecular weight of 5,000, Satake-Ishikawa teaches that modification with a larger PEG molecule is more effective to enhance *in vitro* activity of

rHuG-CSF, and Ishikawa teaches the use of PEG with an average molecular weight of 5,000-20,000. For reasons set forth below, Applicants respectfully disagree.

Assuming *arguendo*, that Satake-Ishikawa and the Ishikawa teach the benefits of modifying rHu-CSF with larger PEG molecules in order to achieve the desired results of improved *in vivo* activity, one of skill in the art would have to be motivated to try this strategy using an entirely different protein, such as TNF (as taught by the Tsutsumi I reference). However, one of ordinary skill in the art is aware of *all art* pertaining to this area and the teachings of all art must be considered for the obviousness analysis, including those references that teach away from the hypothetical combination. In this case, Satake-Ishikawa and Ishikawa suggest using PEG with an average molecular weight of up to 20,000. This is on *an entirely different protein* than that taught in the Tsutsumi I reference and in the Applicants' invention. Tsutsumi I and the Applicants invention involve TNF. However, Tsutsumi I teaches only a PEG with an average molecular weight of 5,000. Critically, other references of Tsutsumi teach away from the use of higher molecular weight PEG, and therefore, one of ordinary skill in the art would not be motivated to use high molecular weight PEG in combination with TNF.

Specifically, Tsutsumi *et al.* (1996) *Brit. J. Cancer* 74:1090-1095 ("Tsutsumi II")(cited by the Applicant (u17)) teaches the use of PEG-modified TNF-α in which the PEG has an average molecular weight of 2,000, 5,000, and 12,000. Notably, however, Tsutsumi II teaches that although TNF modified with PEG having an average molecular weight of 12,000 had an increased antitumor potency, the bioactivity of PEG-modified TNF-α decreased with increasing PEG modification, and this decrease was marked when the

molecular weight of the attached PEG was increased (see Tsutsumi II, page 1093). Moreover, the investigators noted that the coupling reaction between $PEG_{12,000}$ and TNF-α was "extremely limited" probably due to steric hindrance caused by early attached $PEG_{12,000}$ molecules (Tsutsumi II, page 1093). Finally, and critically, the investigators stated "These results strongly indicated that the molecular size of PEG-TNF-α, that is, the steric hindrance determined by the degree of PEG modification as well as the molecular weight of PEG, is a very important factor to consider in designing hybrid TNF-α" (Tsutsumi II, page 1093).

Thus, one of skill in the art would reason that using PEG with a higher average molecular weight, as suggested by the applicants, would not be advisable. First, such high molecular weight PEG would be expected to react even more poorly with TNF-α, as $PEG_{12,000}$ reacted "extremely poorly" due to steric hindrance. Second, high molecular weight PEG would be expected to decrease the bioactivity of TNF-α with increasing PEG modification, and worsen this result as Tsutsumi noted that the downward rate in biological activity was marked in proportion to the PEG molecular weight. Third, high molecular weight PEG would be expected to raise the overall molecular size of the PEG-modified TNF-α, and Tsutsumi noted that "PEG-TNF- α ranging from 100 to 110 kDa, whose specific bioactivity remained above 50% in comparison with native TNF-α was *the most optimal* PEGylation product (Tsutsumi at page 1094, column 1)(emphasis added). In that case, only $PEG_{12,000}$-TNF-α Fr.3 and MPEG-TNF-α (modified with $PEG_{5,000}$) satisfied these requirements. $PEG_{12,000}$-TNF-α Fr.3 had a molecular size of 104,000 and a remaining bioactivity of 85.7% (Tsutsumi at page 1093, last paragraph). Notably, Figure 1a shows than even modest changes in the degree of PEG modification using $PEG_{12,000}$ results in a

precipitous drop in remaining bioactivity. Thus, one of skill in the art would predict that larger PEG molecules would adversely affect remaining bioactivity, contrary to the guidance of Tsutsumi II.

Applicants earnestly submit that the state of the art teaches away from the hypothetical combination suggested by the Office Action and, thus, the claims are not obvious over the prior art. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

B. The Office Action also maintains the rejection of Claims 1 and 8 under 35 U.S.C. § 103(a) as allegedly obvious over Tsutsumi I in view of Satake-Ishikawa and Ishikawa, and further in view of Mark, D.F., *et al., Methods Enzymol.* 154: 403- 414 (1987) ("Mark"). As the hypothetical combination of Tsutsumi I, Satake-Ishikawa and Ishikawa fail to satisfy the legal requirements of obviousness, Mark adds nothing to make up for the fundamental deficiency in the Office Action's obviousness determination.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. U.S.C. § 103(a) over Tsutsumi I in view of Satake-Ishikawa and Ishikawa, and further in view of Mark.

II. Rejection under 35 U.S.C. §112, second paragraph (Indefiniteness)

Claims 1 to 4, 14 to 17, and 24 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term "TNF." Applicant respectfully

traverses the rejection because the cited term conveys a clear and definite meaning to those skilled in the art as reasonably as the subject matter permits.

The Federal Circuit has stated that when "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985)).

In the instant case, the Applicants set forth a definition of TNF at page 5, lines 23-29 through page 6, lines 1-5. Further, the Applicants discuss the activities of TNF in the background of the invention section, and specifically state that TNF was originally named by reference to its biological activity for its ability to kill tumors (Specification, page 2, lines 19-20). The citation to early papers on TNF activities date to 1975 (see Specification, page 2, lines 25-26), indicating that the activities of TNF have been appreciated by those of skill in the art for decades. Thus, one of skill in the art, reading the Specification, would be reasonably apprised as to what is meant by "TNF" and such a definition (given the fact that TNF was traditionally defined by its biological activity as a tumoricidal cytokine) is as precise as the subject matter permits.

Withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

III. Rejection under 35 U.S.C. §112, first paragraph (Written Description)

The Office Action objects to the amendment entered in the Applicants' Response filed October 14, 2003 presumably because the Examiner finds no teaching of the limitation "range of 15,000 to about 40,000" or the limitation "15,000" *in haec verba.*

Applicants respectfully request reconsideration of this rejection in view of the basis of the so-called "Written Description Requirement" and the current case law as developed by the United States Court of Appeals for the Federal Circuit.

In *In re Wertheim*, the Federal Circuit noted that "the function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter *later* claimed by him." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In other words, as restated more recently by the Federal Circuit:

> The purpose of the written description requirement is to prevent an applicant from *later* claiming that he invented that which he did not; the applicant for a patent is therefore required "to recount his invention in such detail that his *future claims can be determined to be encompassed within his original creation.*"

Amgen Inc. v. Hoechst Merion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)(citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (emphasis added).

As is evident from the Federal Circuit's discussion of the Written Description Requirement, the showing of "in possession" refers to whether the Applicant is later trying to claim (*e.g.*, by adding or amending claims) subject matter that was not *encompassed* by the original description. Such is not the case with the present application; the Applicants originally described and claimed the use of PEG having an average molecular weight of

about 10,000 to about 40,000. The limitation "15,000" and the limitation "15,000 to about 40,000" is clearly encompassed by the Applicants' original disclosure.

Applicants earnestly submit that the claims as presented satisfy the Written Description Requirement as the Applicants were clearly in possession of the claimed subject matter at the time of filing, and no issue of late claiming is presented. Withdrawal of the rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

Date: May 17, 2004

Patrick J. Farley, Ph.D.
Registration No. 42,524

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439